Significant role of fat tissue hormones in development of comorbid chronic pancreatitis and obesity

T. N. Hristich
Bukovina State Medical University, Chernovtsy, Ukraine

Key words: chronic pancreatitis, obesity, adipocytokines, low-intensity chronic systemic inflammatory response, type 2 diabetes mellitus, pancreatic cancer

Study the question of disorders of lipid metabolism in chronic pancreatitis (CP), including: with obesity, in recent years attention is paid not only to endocrinologists, but also to gastroenterologists [1, 3, 11], but a number of unresolved issues remain. For example, insufficient attention is paid to consideration of the possible role of the pancreas(pancreas) in the occurrence of metabolic and hormonal disorders obesity, metabolic syndrome (MS), type 2 diabetes mellitus (DM 2tipa) with the view to not e as a universal body carrying not only exocrine but and endocrine function.

In connection with violations in the activity of these functions in CP, both the secretory and endocrine parts of the pancreas are damaged, which is of great importance in the disturbance of homeostasis. The lack of endocrine function of the pancreas is clinically manifested by the manifestation of metabolic disorders. It is believed that it is the endocrine cells of the pancreas that regulate the activity of the exocrine function. External obscure pancreatic failure (especially mild and moderate severity) is observed not only in diseases of the pancreas, including. at CP, type 2 diabetes, but also with osteoporosis, uremia, after surgery on stomach, pancreas, obesity and other pathological states and x.

The main clusters of obesity, MS, type 2 diabetes are the dysfunction of food-eating hormones, the functional state of the liver, the pancreas, microbial ecology of the small and large intestine. Accordingly, a number of problems arise that require a study of their role in the development and progression of certain syndromes and diseases. These include the activation of neuropeptides, dysfunction of the endocannobioid system, eating hormones, the sympathetic nervous system, impaired release of insulin from beta -cells of the pancreas, disruption of the processes of peroxidation and metabolism of liver lipids, the importance of free fatty acids in the development of insulin resistance (IR). In addition, attention is drawn to the study of the significance of microproteinemia, the interaction of hemostasis systems, the role of fibrinolysis, hyperuricemia, nitric oxide, adipokines and other cytokines that determine the common pathogenesis of CP and other diseases of the digestive system, obesity, MS and DM type 2.

Manifestations of MS in diseases of the digestive system, such as IR, dyslipidemia atherogenic origin of abdominal obesity type, moderate arterial hypertension (AH) and metabolic changes, disorders of the central hemodynamics, the tendency to gipokaliygistii, found in 29,1-89,3% of cases. The highest percentage of obesity (89%), IR (75%),dyslipidemia pro atherogenic l I (55%), metabolic changes on ECG (45%) is fixed in CP in combination with erosive

gastritis, gastroesophageal reflux disease (GERD), withcholelithiasis, chronic cholecystitis [10].

One of pancreatic hormones m playing an important role in adaptive processes of the organism, c insulin is read. He is a vascular monomial of p, which in healthy people causes vasodilation, and in pathological conditions (in the case of IR and hyperinsulinemia) — vasoconstriction. Insulin actively participates in energy and lipid metabolism [2], in the development of hypertensive syndrome, incl. at the expense of I increase the expression of the transporter of sodium ions in the epithelial sodium channels reduces the activity of Ca^{2+}-ATPase thereby increases intracellular content of Ca^{2+} in β-cells of the pancreas, which contributes to the formation of compensatory hyperinsulinemia.

Yes Mr. nye processes first reducing sensitivity w t and then disables w t insulin receptors and glucose from food and fats deposited adipose tissue. This further strengthens the IR. Permanent hyperinsulinemia depletes the secretory apparatus β-pancreas cells, which leads to the development of disorders of carbohydrate metabolism: moderate increase the ntsentratsii of glucose in fasting plasma first, and then — after the food load, and finally — a development of type 2 diabetes. In turn, hyperglycemia causes impairment of the function of beta — cells of the pancreas (the effect of glucose toxicity), closing the vicious circle.

On the other hand, hyperinsulinemia inhibits the breakdown of fats, which contributes to the progression of obesity. Studies have shown that a significant increase in the mass of visceral adipose tissue is combined with MS. It is noteworthy that unlike the fat tissue of the other localization it has a wider network of capillaries and directly connects with the portal system, providing opportunities for the systemic effect of adipocytokines on the course of chronic systemic inflammation in the liver and the pancreas [9].

Visceral adipocytes have high density β — adrenergic receptors (especially β_3 types), and corticosteroid androgen receptor and relatively low for the alpha 2 — adrenergicreceptors and receptors to the insulin. T his is determines high sensitivity visceral adipose tissue to lipolytic action and low kateholominov — to antilipolytic effects of insulin (especially in the postprandial period). The reasons for the development of abdominal obesity include age, after 30 years, when the activity of the hypothalamus increases ACTH system with the release of core t Isola, which leads to a long and rad ishney secretion. Because of this, a characteristic fat distribution resembles Cushing's syndrome. In parallel,AH is found and a violation of glucose tolerance, with the possible development of diabetes. It is known that cortisol stimulates cortisol-dependent lipoprotein lipase on capillaries of fat cells of the upper half of the trunk, abdominal wall and visceral fat. As a result, fat storage is increased, hypertrophy of fat cells develops and the char acterial abdominal obesity [5, 12]. In addition, together with insulin, glucagon, adrenaline and hormones of adipose tissue, male and female sex hormones, glucocorticoids, thyroidhormones participate in the regulation of endocrine processes.

In turn, the expansion of adipose tissue activates the renin-angiotensin-aldosterone system, resulting in a decrease in insulin sensitivity, n e pc and m and

p have a Oxidativestress first that affects cellular signals, cell growth, proliferation and expansion of internal ikletochnogo matrix in CP [8]. Excess circulating aldosterone damages the function of β-cells of the pancreas, disrupts the transmission of insulin signal to the cell, reduces the sensitivity of skeletal muscles to insulin, increases production pro-inflammatoryadipokines Ms rovoy cloth forming endothelial dysfunction.

The aim of this review of the literature was to consider the role of fatty tissue hormones in the mechanisms of obesity development, incl. at CP, especially since in recent years obesity has been considered as an independent etiological factor in the development of CP and pancreas cancer [6, 14]. This can be confirmed by the presence of specific transmembrane receptors to leptin, which are detected not only in adipose tissue, liver, kidneys, but also in the pancreas, heart and platelet surface.

Adipokines, secretes adipose tissue, it is not just a reservoir of energy resources in the form of triglycerol (TG), but also a complete endocrine organ. They participate in the regulation of appetite, thermogenesis, activity of pressor and hypotensive systems, in metabolism of fats and carbohydrates, in stimulating the formation of pro-inflammatory cytokines, among which FN O- α It is also considered an adipokin, involved in the formation of chronic systemic inflammation.

The role of adiponectin and leptin in the pathogenesis of obesity has been studied to a greater extent. A study of residual m is adiponectin — glycoprotein hormone which open in 1995-1996., using Myocytes and liver as the main targets of their influence. In these tissues, it improves sensitivity to insulin, has an anti-atherogenic effect. Adiponectinacts via the 5'AMP-protein kinase (AMPA), which inhibits acetyl coenzyme A carboxylase inhibition and removes oxides β- L eniya malonilkoenzimom A, increases the absorption myocytes fatty acids from the blood and the rate of β-oxidation in muscles, stimulates the consumption of glucose and its catabolism in the muscles and liver.

Adiponectin having antiinflammatory, o- angas, cardioprotective and antidiabetic effect. This is confirmed by a negative correlation with the level of glucose, insulin, TG,leptin, FNO-α (inhibiting its secretion). By reducing the level of expression of adiponectin FN O- α in adipocytes increases, facilitating adipose tissue build-up TS through Expro SMAI genes involved in transcription factors lipo — and adipogenesis.

It is believed that FNO-α, produced by adipose tissue, lymphocytes and monocytes is not only responsible for the IR, forming smoldering systemic chronic inflammation,but also dysfunction of β-cells of pancreas, which is undoubtedly one of the main factors that lead to the progression lipoidoza, steatosis with association of CP with obesity, and type 2 diabetes. The concentration of this adipokin, such as apelin, also influences the activation of the production of this cytokine.

Apelin — recently identified ligand for the small intestine and hypothalamus APJ-receptor propeptide comprising 77 amino acid residues. It is split into several shorterpeptides, which are ligands for the aphelin receptors. Synthesized not only in adipocytes, but and in the stomach, heart, small intestine and hypothalamus. When administered into the ventricles of the brain and causing an apelin reduction

in food intake, both in the well-fed and in hungry rats. These data support the possible the role of apelin in the control of eating behavior [20]. To the complex of Apelin- APJ ruetsya expression in the gastrointestinal tract, affecting the exocrine function of the pancreas, participating in the regulation of fibrotic processes in liver, kidney and heart. The hypothesis of a regulatory effect on the complex apelin- APJ fibrotic processes in the pancreas based on the identification of high-expressing collagen alpha-1, 4 collagen and protein levels in mice with CP. In contrast to the ability of apelin to inhibit the processes of fibrosis in theprostate, in the liver it stimulates them [22]. There have been studies indicating that apeline inhibits pancreatic activation of the transcriptional nuclear factor kappa-B in acinarand islet cells of the pancreas [27], which demonstrates the protective effect of apelin on pancreas tissue in the presence of chronic sluggish inflammation. That e st,apelinergicheskaya system is an important component that allows to stop inflammatory and fibrotic changes in CP [18], caused by t.ch. hypoxia, ischemia of the organ [17]. Some authors consider the system of apelin — APJ as the main mediator of oxidative stress in various tissues, incl. in endotheliocytes, which suggests that the endogenous peptide of amphetamine can be a factor in the occurrence of pathologies associated with the mechanisms of development of not only non-alcoholic liver disease, steatosis of the pancreas,but also the formation of MI, obesity, MS, T2DM. Its role in the formation of cardiovascular pathology (myocardial hypertrophy, heart failure, arterial hypertension, especially in type 2 diabetes) is noted, which is important for explaining the mechanisms that determine the clinical picture of CP associated with obesity, type 2 diabetes, MS, taking into account complications from the side concomitant diseases.

An increase in the volume of visceral adipose tissue results in a systemic release of the resistin protein and pro-atherogenic interleukins. Enriched with cysteine 12.5 kDa,the resistin protein and molecules similar to it are a family of proteins that take part in the processes of inflammation and development of resistance to insulin action. He is an antagonist adiponectin. It has both a paracrine and a telekinic action, since it has receptors, both in the fat tissue and in the liver. Level Resistin increases with increasing body weight. A direct relationship between the level of resistin and levels of low density lipoproteins (LDL), triglycerides, fasting glucose, C-reactive protein (CRP) and anthropometric data (BMI, waist circumference w and thorax) and inverse relationship — with the level of lipoproteins high density (HDL), which is very important for clinical practice. It discusses the potential role of this adipokine as a link between obesity and type 2 diabetes [25], as in conditions of hyperinsulinemia and reduced sensitivity to insulin in adipose tissue, particularly visceral, yc ilivaetsya and lipolysis are increased delivery of free fatty acids in the liver. The liver is the first target organ of resistance, leading to the development of hepatic IR [13]. As a result, Zoom ivaetsya LDL cholesterol, hypertriglyceridemia, I formed and reducing the content of e aetsya HDL (which represents the "atherogenic th triad"). Consequently, p ezistin can serve an indicator for determining the severity of TS, obesity, atherosclerosis, systemic inflammation intensity andcomorbidity with CP.

Resistin serves as a promoter of maturation of fat cells and acts as a and the utricine Education regulator prodiabet Ogen factors in adipose tissue. In addition, this adipocyte-specific hormone can be characterized as proliferative, anti-apoptotic, pro-inflammatory and a proangiogenic regulator [15, 16].

Resistin was isolated in 2001. It is secreted predominantly preadipocytes, less mature adipocytes of abdominal localization and macrophages [26]. Exactly activated macrophages are the source of adult serum resistin, but the prerequisite is the presence of cytokines — TNF- α and IL-6 [19, 21], which testifies in favor of not only local (in adipose tissue), but and systemic chronic low urs character n e Vågå inflammatory process.

There are currently open and I izuchayuts point applications such as the pancreas hormone adipolin — new adipokine, has anti-inflammatory properties andglyukozoponizhayuschimi, regulating the metabolism of carbohydrates and lipids in the liver and adipose tissue and reducing systemic inflammation.

The interest is represented by visfatin — a protein hormone, discovered in 2004. It is produced by visceral adipocytes and acts on those tissues in which there are insulinreceptors, although its receptors are different from insulin. Since been consistent, these hormones-not sinnergisty compete for binding sites on the membranes of target cells. TheIS F ting stimulates phosphorylation inside cell proteins by tyrosine, including insulin receptor protein substrates. His level increases in proportion to the degree of obesity, he controls the expression of adiponectin [24]. In a recent study, it was shown that visfatin activates human lymphocytes, enhancing the production of proinflammatory cytokinesIL-1β, TNF-α and IL-6, as well as the synthesis of co-stimulating transmembrane molecules CD54, CD40 and CD80 [23].

Based on the published literature, most of the visceral adipose tissue hormones affect the pancreas tissue through the immune system reaction, supporting the persistence of chronic systemic inflammation. Along with others, such hormones adipose tissue, as leptin, resistin, visfatin, adiponectin, adeline, adipolin. Various factors leading to the development of inflammatory changes with the death of acinar cells and the replacement of their adipocytes, contribute to the formation of fatty dystrophy (replacement — fatty replacement) followed by the development of steatosis of the pancreas. Steatosis is a broader concept that includes parenchymal fat distribution (in acinar and islet cells), as well as lipomatosis Pancreas, in t.ch. Arose on the background of inflammatory changes taking place in the organ. The development of such processes can eventually lead to the formation of fatty disease of the pancreas. T Ermin "nonalcoholic Separated Separated fat pancreas diseases v 'determines the relationship of the the state of obesity and other components of MS, excluding congenital pathology. In this connection, non-alcoholic fatty disease of the pancreas should be on a par with non-alcoholic fatty liver disease component MS [4, 7, 13]. This opinion is also supported by a significant increase in the number of patients with MI on the background of steatosis Pancreas. In thevillage annom to beam e consider the junction of steatosis and dysfunction of the insular apparatus against the background of the triglycerides lipotoxic effect. It is consideredalso the possibility of a paracrine effects on adipocytes pancreas

insular first apparatus and the formation of dyslipidemia as mechanisms of combined currents KP and obesity.Presented data indicate sufficient activity and Eni and expand the scope and scientific studies on the association of steatosis The level of adipocytokines and the incremental function of the pancreas in the context of the possible pathogenesis of non-alcoholic fatty disease of the pancreas and its participation in the progression of MS.

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Significant role of fat tissue hormones in development of comorbid chronic pancreatitis and obesity

T. N. Hristich
Bukovina State Medical University, Chernovtsy, Ukraine

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Aim is to consider the role of hormones in the adipose tissue of obesity mechanisms of metabolic syndrome, type 2 diabetes mellitus in chronic pancreatitis.

Materials and methods. Literature review indicates the value of visceral fat in the development of insulin resistance, dyslipidemia, including atherogenic one, taking into account the possible infiltration of pancreatic tissue by adipocytes. Participation of some adipocytokines of adipose tissue in the development of obesity in chronic pancreatitis is highlighted. It is shown that in some cases the hormones of visceral adipose tissue, penetrating through the portal vein to the liver and then to the pancreas, aggravated the course of systemic chronic inflammation typical for the inherent chronic pancreatitis, formed steatosis and promoted development of fatty disease of the pancreas.

Conclusion. Literary sources show the leading role of visceral adipose tissue and its hormones in the formation of obesity in chronic pancreatitis. Lipoidosis or steatosis develop due to the infiltration of the liver and pancreatic tissue by adipocytes. Upon the progression of the type 2 diabetes, fatty liver or pancreatic disease, or cancer of these organs may develop. Consequently, there is a strong need for a serious differentiated preventive and curative measures aimed at promoting a healthy lifestyle to improve the quality of life of patients suffering from chronic pancreatitis.